1186-5 Independent Hemodynamic Effects of Irregularly Paced Ventricular Rate Following AV Nodal Ablation During Atrial Fibrillation

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Background: It is known that AV nodal (AVN) ablation with right ventricular pacing at regular rate (R) produced better hemodynamics compared to irregular pacing (IR) at the same average rate during atrial fibrillation (AF). However these observations were made at fast ventricular rates (VR) similar to those present in AF. We test the role of the paced ventricular irregularity at different average VR. **Methods and Results:** AF was induced and maintained in 12 dogs. Selective AVN vagal stimulation was delivered to slow VR to 125%, 100%, 80%, and 67% of the sinus rate (SR). The AVN was then ablated. The IR and R were performed using the 4 sets of saved RR intervals, and the corresponding averages respectively. For each level of VR, R was superior to IR (Table). This difference, however, was significantly attenuated when VR was slowed to 67% SR. **Conclusion:** Irregularity of VR remains an independent factor in the deterioration of hemodynamics in AF. Its role is diminished with progressive slowing of VR.

VR (bpm), % SR, and Mode (R or IR)	LVSP (mmHg)	LVEDP (mmHg)	+dLVP/dt (mmHg/sec)	-dLVP/dt (mmHg/sec)	CO (L/min)	Tau (msec)
155±20, 125%, (R)	78±10	6.4±1.3*	1380±308*	-1169±321*	1.95±0.37*	51±7
156±20, 125%, (IR)	75±12	8.5±2.3	1255±262	-858±280	1.84±0.39	53±7
125±18, 100%, (R)	85±13*	7.1±1.6*	1362±226*	-1267±343*	1.84±0.34*	49±5*
125±18, 100%, (IR)	80±11	8.6±2.4	1271±187	-1005±258	1.74±0.35	52±5
99±13, 80%, (R)	86±12*	6.9±1.4*	1277±151	-1278±227*	1.76±0.31*	48±7*
99±13, 80%, (IR)	82±10	7.6±1.4	1272±206	-1166±295	1.71±0.32	51±8
84±11, 67%, (R)	88±13	7.2±1.4	1390±275	-1261±298*	1.80±0.30	49±7
84±11, 67%, (IR)	87±13	8.0±1.8	1318±204	-1183±243	1.74±0.29	50±7

LVSP / LVEDP: Left ventricular systolic / diastolic pressure; dp/dt max rate of change of LV pressure; CO: Cardiac output, Tau: time constant of relaxation. * P< 0.05 for R vs IR at same VR.

1186-6 Spatial Heterogeneity of Electrical Restitution During Regional Ischemia in Rabbit Ventricles: Effects on Wavebreaks During Ventricular Fibrillation

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Background: The action potential duration restitution (APDR) is considered a major determinant in the initiation and maintenance of ventricular fibrillation (VF). However, the effects of acute regional ischemia on APDR are poorly understood. Methods: We performed optical mapping studies with di-4ANEPPS in 12 Langendorff-perfused rabbit hearts. Branches of left anterior descending or circumflex coronary artery were ligated to create regional ischemia. Sham ligation was done in 2 rabbit hearts. LV anterior wall was optically mapped during pacing and during VF before, 30 and 60 min after ischemia. We defined the border zone (BZ) as the area with a gradient of APD between the ischemic zone (IZ) and non-ischemic zone (NIZ) in the APD50 map. Twenty-Five APD restitution curves on the LV anterior wall were constructed simultaneously before and 30, 60 min after ischemia. The number of wavebreaks during VF was also analyzed. Results: The area with ischemia (BZ+IZ) occupied 33.2 ± 13.6% of the mapped field. In ischemic area (BZ+IZ), the APDR slope progressively flattened (lowest max. slope: baseline, 1.0±0.5; 30 min, 0.6±0.3; 60 min, 0.6±0.3; p<.05) while in NIZ, the APDR slope progressively steepened (highest max. slope: baseline, 1.7±0.7; 30 min, 2.4±0.7; 60 min, 2.6±1.0; p<.001), producing progressively increased spatial heterogeneity of APDR slope (SD of max. slope: baseline, 0.18±0.11; 30 min, 0.43±0.13; 60 min, 0.53±0.21; p<.001). There was no significant change in APDR characteristics in sham ligation group. The dispersion of APD50 (baseline, 8.5±3; 30 min, 29±14; 60 min, 31±13 ms; p<.01) and the wavebreak number of VF (baseline, 4.2±1.6; 30 min 11.9±5.8; 60 min 15.5±10.9; p<.001) were significantly increased after ischemia. The spatial heterogeneity of APDR and longest DI with slope>1, but not dispersion of APD, significantly correlated with the wavebreak number of VF. Conclusions: The spatial heterogeneity of APDR is increased by the presence of regional ischemia, resulted in increased wavebreaks during VF. The dynamic changes of APDR characteristics are more important than pre-existing or ischemia-induced APD dispersion in determining the wavebreaks of VF during acute regional ischemia.

1186-7 Persistent Automaticity as a Mechanism of Ventricular Defibrillation Failure

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Background: Electrical storm (ES) describes the phenomenon of rapidly clustering ventricular fibrillation (VF) that necessitates multiple defibrillation (DF) shocks. There exists no animal model for ES. We hypothesized that a persistent fast firing automatic focus can result in ES.

Methods and Results: We studied 14 isolated perfused normal swine right ventricles (RV). Local injection of aconitine (100mg) either in the middle (n=9), or in the edge (n=5) of the RV induced ventricular tachycardia (VT) followed by VF in all RVs. The activation cycle length (ACL) of VT before VT-VF transition was 166 ± 37ms. Continuous electrogram recording and optical mapping (CCD camera, di-4ANEPPS) were performed during DF with biphasic shocks (6 ms duration) generated by a Ventritex HVS-02 defibrillator. The success rate of DF was tested before and after aconitine injection. Before injection, DF was successful in terminating all electrical activities with one (n=12) and two shocks (n=2) at 314 ± 36 V (range 300-400 V). In comparison, DF shocks (n=5.8 ± 1.1) with average amplitudes of 635 ± 75 V (range 500-700 V) lead to conversion of VF to VT in 14 of 14 RVs after aconitine injection. In 12 out of 14 RVs the VT lasted for 7.5 ± 5 seconds before spontaneous conversion back to VF. VT persisted for > 20 minutes in the remaining 2 aconitine-injected RVs without VF conversion. Optical mapping during DF revealed two mechanisms of post shock VT to VF transition. First, acceleration of the rate of focal activation from aconitine site leads to wavebreak and multiple wavelets VF. Second, the focal activation emerging from the aconitine site induces rotating phase singularity that deteriorates to VF by a spiral breakdown mechanism. After aconitine site was excised (n=5), DF shocks (300 V – 400 V) successfully terminated VF.

Conclusions: Aconitine injection into swine RV induces persistent focal activation that is resistant to DF shocks. This focus serves as a trigger for recurrent VF. Excision of this focus allows successful DF. This animal model suggests that a shock-resistant automatic or triggered focus underlie the mechanisms of ES, and successful treatment can be achieved only when the focus is eliminated or suppressed.

1186-8 Ischemia Precipitates Ventricular Tachyarrhythmias in Transgenic Mice Overexpressing Calcium-Independent Phospholipase A2β (IPLA2β) That Are Ablated by Mechanism-Based Inhibition of Phospholipase A2 Activity

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Calcium-independent phospholipase A2(iPLA2β) has been implicated in ischemia-induced ventricular tachyarrhythmias. To determine whether increased myocardial iPLA2β activity promotes arrhythmogenesis during ischemia, mice overexpressing iPLA2β in a cardiac myocyte specific fashion were prepared using an αMHC promoter proximal to the iPLA2β gene. Transgenic mice exhibited a 20-fold increase in iPLA2β mass and activity in myocardium and profound alterations in polar and nonpolar lipid profiles. During 30 min of myocardial ischemia induced in isolated, Langendorf-perfused hearts by occlusion of the left anterior descending coronary artery, spontaneous ventricular premature contractions occurred more frequently in iPLA2β overexpressors (n=24) than in wild-type control hearts (n=19, p=0.0003). Moreover, spontaneous ventricular tachycardia occurred as a single episode in one of 19 wild-type hearts, but as multiple episodes in 9 of 24 IPLA2β overexpressor hearts (p=0.002). Pretreatment with the mechanism-based inhibitor, BEL (10 μM), ablated both spontaneous ventricular premature contractions and tachycardia. We conclude that the iPLA2β-catalyzed hydrolysis of membrane phospholipids can precipitate lethal ventricular tachycardia in ischemic myocardium.

1186-9 Cyclic GMP-Dependent Protein Kinase Type I (PKG I) Mediates cGMP Inhibition but Not Muscarinic Inhibition of Single L-Type Ca^{2+}-Channel Activity in Cardiac Myocytes

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Background: In cardiomyocytes, the contribution of nitric oxide (NO) to the intracellular signal transduction of the muscarinic receptor is discussed controversially. NO increases intracellular cGMP, which activates the cGMP-dependent protein kinase type I (PKG I). PKG I inhibits the L-type Ca^{2+} channel (LCC). We addressed the role of PKG I in the signal transduction from the muscarinic receptor to the LCC.

Methods: Transgenic mice (TG), in which PKG I was placed under the control of the cardiomyocyte-specific α MHC-promotor, were generated. Single LCC activity was assessed by patch clamp in the cell-attached configuration in isolated ventricular myocytes from wild-type mice (WT) and from TG overexpressing PKG I approx. 50-fold in the myocardium.

Results: Basal LCC activity was similar in myocytes from WT (n=53) and TG (n=52), i.e. there were no significant differences in the basal mean ensemble average current (I), mean open probability (p_o) and mean availability to open upon depolarisation (f_b). Activation of PKG I in myocytes from WT using 8-Br-cGMP (1 mmol/L) did not influence basal LCC activity (n=7). Activation of PKG I in myocytes from TG, however, significantly decreased LCC activity (I -50.7±5.4 %; p_o -37.0±9.2 %, f_b -31.0±8.4 %; n = 9, data indi-